

# Cells to Surgery Quiz: December 2021

Fabio Stefano Frech<sup>1</sup>, Loren Hernandez<sup>1</sup>, Ali Rajabi-Estarabadi<sup>1,2</sup> and Keyvan Nouri<sup>1</sup>

*Journal of Investigative Dermatology* (2021) **141**, e147–e154; doi:10.1016/j.jid.2021.10.014



## WHAT IS YOUR DIAGNOSIS?



**Figure 1.** Image reprinted from *Journal of the American Academy of Dermatology* 2015;73:529–31, with permission from Elsevier.

*Editorial note: Welcome to the Journal of Investigative Dermatology (JID) Cells to Surgery Quiz. In this monthly online-only quiz, the first question (“What is your diagnosis?”) relates to the clinical image shown, while additional questions concern the findings reported in the JID article by Wang et al. (2021) (<https://doi.org/10.1016/j.jid.2021.07.164>).*

Detailed answers and a list of relevant references are available following the Quiz Questions below.

## QUIZ QUESTIONS

### 1. What is your diagnosis?

- a. Dermal melanocytic nevus
- b. Acrochordon
- c. Lipoma
- d. Cutaneous neurofibroma (CN)
- e. Fibroma

<sup>1</sup>Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, Miller School of Medicine, University of Miami, Miami, Florida, USA; and <sup>2</sup>Department of Biochemistry & Molecular Biology, Miller School of Medicine, University of Miami, Miami, Florida, USA

Correspondence: Keyvan Nouri, Dr. Philip Frost Department of Dermatology and Cutaneous Surgery, Miller School of Medicine, University of Miami, 1150 Northwest 14th Street, 5th Floor, Unit 500, Miami, Florida 33136, USA. E-mail: [knouri@med.miami.edu](mailto:knouri@med.miami.edu)

2. **What is false about the management and/or prognosis of cutaneous and plexiform neurofibroma (PNF)?**
  - a. CNs should not be removed, whether the patient has neurofibromatosis type 1 or not, unless there is a reason such as pain, bleeding, interference with function, or disfigurement.
  - b. The effectiveness of selumetinib in the treatment of CNs is approved by Food and Drug Administration.
  - c. Various options for removal, such as surgery, laser removal, or electrodesiccation, are available.
  - d. Selumetinib can induce tumor regression in PNFs.
  - e. Surgical resection of PNF is limited to debulking of a specific area of a large lesion.
  
3. **Wang et al. (2021) evaluated phosphorylated extracellular signal–regulated kinase (p-ERK) and phosphorylated MAPK/extracellular signal–regulated kinase kinase (MEK) (p-MEK) expression in PNFs and its association with clinicopathological parameters. All of the following are consistent with their findings, except:**
  - a. p-MEK/p-ERK expression heterogeneity was observed in PNF tissues and cell lines.
  - b. PNF cell lines were NOT responsive to MEK inhibitor.
  - c. TAK-733–resistant cells exhibited increased survival abilities compared with parental cell lines.
  - d. Dinaciclib was identified as a promising agent in combination with TAK-733.
  - e. The dinaciclib in combination with TAK-733 demonstrated efficacy in treating patient-derived xenograft PNF mouse model.

See following pages for detailed answers

**DETAILED ANSWERS****1. What is your diagnosis?****CORRECT ANSWER: d. Cutaneous neurofibroma (CN)**

Neurofibromas are a form of benign, peripheral nerve sheath tumors that are composed of fibroblasts, Schwann cells, immune cells such as mast cells, and other nerve elements (Allaway et al., 2018; Ferner and O'Doherty, 2002; Ortonne et al., 2018). They are embedded in a collagenous extracellular matrix and can be categorized according to their anatomic location, such as cutaneous and subcutaneous neurofibromas, intraneural neurofibromas, and plexiform neurofibromas (PNFs) (Jouhilahti et al., 2011). They may also be localized (Lassmann et al., 1977; Woodruff, 1999) or diffuse (Shiurba et al., 1984). They have no predilection for sex, race, or ethnicity, with an overwhelming majority occurring sporadically. Those that do not occur sporadically (approximately 10%) have a syndromic association with neurofibromatosis type 1 (NF1) or type 2 (Weiss, 2009). A deletion in the *NF1* (Abramowicz and Gos, 2014) gene, which codes for the tumor suppressor neurofibromin on chromosome 17q11.2, is the cause of neurofibromas in both sporadic and syndromic cases. This deletion results in a loss of RAS/MAPK signaling pathways involved in cell proliferation and differentiation (Abramowicz and Gos, 2014). When syndromic neurofibromas occur, there is a germline mutation in the *NF1* gene. In contrast, in sporadic cases of neurofibromas, only the cell lineages affected will carry the *NF1* mutation. Clinically, CNs appear as well-circumscribed lesions that may be either nodules or plaques (Jouhilahti et al., 2011). CNs may be nascent, flat, sessile, globular, or pedunculated according to one proposed classification system (Riccardi, 1992). Nascent neurofibromas cannot be detected by visual inspection or skin palpation but are recognized by imaging techniques (Riccardi, 1992). Flat CNs range in size from 0.5 to 12 mm and are visible by inspection. They may be slightly raised above the skin surface with either increased or decreased pigmentation compared with the surrounding skin (Riccardi, 1992). Sessile CNs are typically raised with a noticeable apex, which may reach 8–10 mm above the skin (Riccardi, 1992). Erythema or hyperpigmentation may be present, and they are usually 1 mm to 10–12 mm in diameter. Globular CNs are typically 20–30 mm in diameter with a maximum height of similar measure. Pedunculated CNs contain a stalk, typically 1–3 mm in diameter and a few millimeters long, which connects the more superficial portion (5–25 mm) above the surface of the skin with the deeper portion below (Riccardi, 1992). Clinically, individuals with CNs may be asymptomatic. However, 20% of patients with NF1 report pruritus (Brenaut et al., 2016). The underlying pathophysiology is not currently understood. Patients may also consider their CNs to be

aesthetically displeasing. Immunohistochemically, neurofibromas may stain positively for S-100 and Sox10, CD34, neurofilament protein, acid mucopolysaccharides, and epithelial membrane antigen (Jokinen and Argenyi, 2010; Magro et al., 2010; Yeh and McCalmont, 2011). CNs are treated by surgical excision of the lesion. Less invasive surgical methods used in the treatment of neurofibromas include laser-based excision, radiofrequency ablation, photodynamic therapy, and electrodesiccation (Kim et al., 2016; Kriechbaumer et al., 2014; Lutterodt et al., 2016). However, given that they are benign, these lesions should not be removed unless a patient expresses pain, discomfort, and/or physical disfigurement.

**Discussion of incorrect answers:**

- a. **Dermal melanocytic nevus:** A melanocytic nevus is a benign proliferation of nevus cells, which are a subset of melanocytes (Kincannon and Boutzale, 1999). These cells do not contain dendrites and are able to produce melanin (Lever and Schaumburg-Lever, 1990). Melanocytic nevi may be categorized according to whether they are congenital or acquired, with acquired nevi being subdivided by the location of the nevus cells (Kincannon and Boutzale, 1999). That is, in a dermal melanocytic nevus, the nevus cells are clustered in the dermal layer. Predisposing factors include a familial history of multiple nevi because it has been shown that germline polymorphisms may affect the amount and morphology of nevi (Orlow et al., 2015), the amount of childhood sun exposure (Aalborg et al., 2009; Dulon et al., 2002; Harrison et al., 2008; Oliveria et al., 2009; Wiecker et al., 2003), and skin type (De Giorgi et al., 2018; Luther et al., 1996; Schaffer, 2015; Wiecker et al., 2003) because more nevi are found in patients with less skin pigmentation. Dermal melanocytic nevi may range in color from being that of one's skin tone to tan. They are less pigmented than other forms of nevus because nevus cells present in the dermal layer are no longer able to produce melanin (Marks and Miller, 2019). Dermal melanocytic nevi may be dome shaped, pedunculated, or papillomatous and have a rubbery texture on palpation (Rogers et al., 2016). Because most of these nevi are benign and remain so, there is no treatment necessary. Dermal melanocytic nevi are followed through observation for any potential changes, and those patients with multiple nevi are followed with periodic skin examinations.
- b. **Acrochordon:** Acrochordons are benign, pedunculated lesions of the skin. In layman's terms, they are known as skin tags. Their etiology is unknown, but it has been thought that they occur in areas where elastic tissue is scant—this results in atrophic

lesions (Belgam Syed et al., 2021). Studies have shown that there is an association with insulin resistance and obesity as well as trauma (El Safoury et al., 2011; Ragunatha et al., 2011). They are common skin lesions with a prevalence of 46% in the general population and increase with greater age (Belgam Syed et al., 2021). Acrochordons are typically found in intertriginous areas, such as the axilla, neck, and inguinal folds. Although they are mostly asymptomatic, they can become bothersome and pruritic as well as become entangled with clothing and/or jewelry. Given that they are benign, they can be removed for cosmetic purposes through snip excision, cryotherapy, shave excision, or electrodesiccation.

- c. **Lipoma:** Lipomas are benign, subcutaneous tumors of adipocytes (Charifa et al., 2021; Creytens, 2019; Tong et al., 2020). They are relatively common and can be found where normal adipocytes are present. Enclosed in a fibrous capsule, they are typically soft and painless mesenchymal nodules without a clear etiology. Some speculate that trauma plays a role in their formation because it is known that trauma-induced cytokine release stimulates the differentiation and maturation of adipocytes (Aust et al., 2007). Their incidence is increased in patients with hyperlipidemia, obesity, and diabetes mellitus (Kolb et al., 2021). There is a slight predilection for males, and they can occur at any age (Kolb et al., 2021). However, most often, they are discovered in the fourth to sixth decades of life (Fornage and Tassin, 1991). Lipomas grow slowly and may grow to be 2–3 cm in the final size, although there are lipomas that may grow beyond that size and reach >10 cm (Allen et al., 2007). Histopathologically, lipomas consist of normal-appearing adipocytes and fibrous connective tissue (Burt and Huang, 2017). Given their benign nature, lipomas may be observed longitudinally. If treatment is desired, usually for cosmetic reasons, they can be surgically excised (Salam, 2002).
- e. **Fibroma:** Fibromas are benign growths characterized by the presence of fibroblastic and myofibroblastic cells (Lacka and Nasierowska-Guttmejer, 2019). These growths may be categorized according to the patient's age of onset, such as in adult or juvenile fibromatoses. Juvenile fibromatoses include congenital generalized fibromatosis, aponeurotic fibroma, infantile digital fibromatosis, fibromatosis colli, and dermatofibrosis lenticularis. Adult fibromatoses are subdivided into superficial and deep, with some of the superficial fibromatoses being palmar and plantar fibromatosis, dermatofibromas, nodular fasciitis, and elastofibromas (Walker et al.,

2012). Some of the deep fibromatoses include extra-abdominal, abdominal, and intra-abdominal fibromatosis (Ganeshan et al., 2019). The etiology of these growths is currently unknown. Some postulate that a progenitor mesenchymal cell may be influenced by hormones such as estrogen, trauma, and/or pregnancy to become this tumor (Fiore et al., 2016, 2009; Kasper et al., 2017; Koskenvuo et al., 2017). Histologically, both superficial and deep growths are relatively similar. The WNT signaling pathway is altered in both forms. However, the superficial form does not contain mutations in the  $\beta$ -catenin or APC gene (Lacka and Nasierowska-Guttmejer, 2019). Superficial fibromas typically grow at a slow rate and are small in size.

### 2. What is false about the management and/or prognosis of cutaneous and plexiform neurofibroma (PNF)?

**CORRECT ANSWER: b. The effectiveness of selumetinib in the treatment of CNs is approved by Food and Drug Administration.**

Currently, there are no Food and Drug Administration (FDA)-approved oral or topical therapies for the treatment of CNs. The standard of care for the treatment of symptomatic CNs is the physical removal of individual lesions that are burdensome to the patient (Chamseddin and Le, 2019). One of the known pathophysiologic mechanisms that are linked to the rise of CNs is the RAF–MAPK/extracellular signal–regulated kinase (ERK) kinase (MEK)–ERK pathway, which becomes activated by unregulated RAS (Chamseddin and Le, 2019). Combination therapy with selumetinib has been shown to be effective in treating specific types of nonsquamous nonsmall cell lung cancer and malignant peripheral nerve sheath tumors (Ahsan et al., 2016; Melosky et al., 2019). The mechanism of action of selumetinib is through the inhibition of MEK1/2, involved in the pathway mentioned earlier that is linked to the development of neurofibromas (Markham and Keam, 2020). Currently, a pilot phase 2 trial assessing the effectiveness of selumetinib for the treatment of NF1 and CNs is currently underway (National Cancer Institute, 2016). The trial has two main objectives: primarily, the authors want to determine whether the use of selumetinib can result in the shrinkage of CNs; secondarily, the authors want to determine the effects of selumetinib on target inhibition on CNs by assessing the levels of phosphorylated ERK (p-ERK) and phosphorylated protein kinase B before and after treatment (National Cancer Institute, 2016). Enrolled patients receive selumetinib orally twice daily for a cycle of 28 days for up to 24 cycles in the absence of disease progression or

unacceptable adverse outcomes. After completion of treatment, patients are followed up every 4 months for 1 year (National Cancer Institute, 2016).

Other systemic therapies that have been investigated for the treatment of CNs and PNFs include histamine receptor antagonists, stem-molecule factor receptor (c-KIT) inhibitors, and VEGF inhibitors (Massachusetts General Hospital, 2008; Riccardi, 1993, 1987; Robertson et al., 2012). Although not yet proven to achieve a reduction in CNs growth and proliferation, ketotifen has been shown to be effective in reducing symptoms of pain and pruritis through its H<sub>1</sub> histamine antagonist and mast cell stabilizing properties (Riccardi, 1993, 1987). In an open-label pilot phase 2 trial, imatinib (a small molecule c-KIT inhibitor) was shown to cause regression of disease in 26% of patients with PNFs caused by NF1 (Robertson et al., 2012). This trial did not assess the effect of imatinib in CNs. A VEGF antibody, ranibizumab, is currently being studied to determine whether inhibition of VEGF signaling causes tumor volume shrinkage and alterations in interstitial fluid pressure within CNs (Massachusetts General Hospital, 2008). The lack of evolution and quiescent nature of mature CNs suggests that further studies might benefit from focusing on the prevention of CN growth at an earlier period of development rather than on reduction in size at later stages (Allaway et al., 2018; Chamseddin and Le, 2019).

#### Discussion of incorrect answers:

- a. **CNs should not be removed, whether the patient has NF1 or not, unless there is a reason such as pain, bleeding, interference with function, or disfigurement:** Given their benign histology composed of a variety of nonmalignant cells and elements, CNs can be left untreated, and reassurance should be provided to the patient. Even though CNs can be asymptomatic, up to 20% of patients can complain of pruritis that is localized to one or more neurofibromas (Ortonne et al., 2018). In addition, a lower QOL has been shown to be associated with visibility and disease severity of CNs (Vranceanu et al., 2013). If patients are symptomatic or have a significant cosmetic burden, many treatment modalities exist such as surgical excision, electrodesiccation, photocoagulation, and laser treatment (Chamseddin and Le, 2019). These treatment options can be offered in an individualized manner depending on a variety of factors, including preferred esthetic outcome, the burden of disease, and tumor size and location (Chamseddin and Le, 2019; Chamseddin et al., 2019).
- c. **Various options for removal, such as surgery, laser removal, or electrodesiccation, are available:** Even though CNs can be left untreated owing to their benign nature, some patients might choose to have them physically removed for various reasons such as pain, itching, bleeding, or cosmetic burden. As a result, there are various methods of surgical removal of CNs that may be offered to patients with unwanted CNs (Chamseddin and Le, 2019). For cosmetically sensitive areas, surgical excision, photocoagulation, or a modified biopsy removal method can be used depending on the size and morphology of the lesion. For lesions >2 cm and of a globular morphology, surgical excision is preferred; otherwise, for lesions <2 cm and of any morphology, photocoagulation or a modified biopsy method can be performed (Chamseddin and Le, 2019). For patients with multiple CNs in cosmetically insensitive areas such as the extremities and trunk, carbon dioxide (CO<sub>2</sub>) lasers and electrodesiccation are sufficient for treatment (Becker, 1991; Lutterodt et al., 2016). Although CO<sub>2</sub> lasers can be efficient at removing CNs, it is important that patients are aware that hypertrophic scarring is a possible unintended side effect of the procedure (Ostertag et al., 2002).
- d. **Selumetinib can induce tumor regression in PNFs:** In 2020, selumetinib was approved by the FDA for use in pediatric patients aged ≥2 years with NF1 who have symptomatic, inoperable PNFs (FDA, 2020). A phase 1 trial on children aged 3–18 years to evaluate maximum tolerable dose, plasma pharmacokinetics, and response to treatment was performed (Dombi et al., 2016). Patients received 10-mg and 25-mg tablets every 12 hours on a continuous dosing schedule for 28-day cycles, and a volumetric magnetic resonance imaging (MRI) analysis was used to measure response to treatment. Dosing was calculated based on body-surface area using a nomogram. Evaluation of response to treatment revealed a >20% decrease in tumor volume for 71% of participants (Dombi et al., 2016). An open-label, phase 2 trial on children aged 2–18 years was completed to evaluate the clinical benefit and objective response rate of selumetinib for inoperable PNFs (Gross et al., 2020). A total of 50 patients received 25 mg/m<sup>2</sup> of body surface area every 12 hours for 28-day cycles. Of the 50 patients, 34 had a confirmed partial response, and 28 of those patients had a response lasting >1 year. In addition, there were clinically meaningful improvements in areas related to tumor pain intensity, pain in daily functioning, overall health-related QOL, functional strength, and range of motion (Gross et al., 2020).
- e. **Surgical resection of PNF is limited to debulking of a specific area of a large lesion:** Unlike CNs, PNFs have about a 5% risk for malignant transformation (Gutmann, 1998). PNFs can be classified into three different categories on the basis of growth

characteristics identified by MRI: superficial, displacing, and invasive (Friedrich et al., 2005a). For superficial PNFs, total or subtotal resection is possible without negatively affecting functionality (Friedrich et al., 2005a, 2005b). Invasive PNFs are more challenging to resect owing to the risks of injuring adjacent structures (Friedrich et al., 2005a). In addition, the histology of the tumor will affect the surgical approach used for resection. A PNF that has undergone malignant transformation requires margins free of tumor and can sometimes only be realistically achieved through amputation of the affected area owing to the extensive functional nerve damage (Canavese and Krajbich, 2011). A benign PNF can be treated with marginal resection; yet, depending on the location and extent of invasion, the surgical resection is limited to debulking a certain area of a larger lesion to ameliorate pain, improve cosmesis, and recover functionality (Canavese and Krajbich, 2011; Vetrano et al., 2019).

3. Wang et al. (2021) evaluated phosphorylated extracellular signal-regulated kinase (p-ERK) and phosphorylated MAPK/extracellular signal-regulated kinase (MEK) (p-MEK) expression in PNFs and its association with clinicopathological parameters. All of the following are consistent with their findings, except:

**CORRECT ANSWER: b. PNF cell lines were NOT responsive to MEK inhibitor.**

Wang et al. (2021) investigated how PNF cells respond to different MEK inhibitors (MEKis) in vitro. They evaluated the effectiveness of selumetinib, trametinib, PD0325901, TAK-733, cobimetinib, and refametinib in three *NF1*-deficient PNF cell lines and one Schwann cell line as a control after 72 hours of incubation. The MEKi TAK-733, trametinib, and cobimetinib showed to be more effective for inhibiting PNF cell viability than the other three inhibitors. In addition, these agents exhibited a more sensitive trend to *NF1*-deficient PNFs, with a lower half maximal inhibitory concentration level, than the normal Schwann cell control.

**Discussion of incorrect answers:**

- a. **p-MEK/p-ERK expression heterogeneity was observed in PNF tissues and cell lines:** Wang et al. (2021) evaluated cancer molecular heterogeneity by employing a PNF tissue microarray containing two tissue cores per tumor. They evaluated different expression intensities of different markers, including p-MEK, p-ERK, MEK, and ERK, in the PNF tissue microarray. They showed that the p-MEK and p-ERK protein levels in different clinical PNF tumor tissues and cell lines were heterogeneous, which may provide an explanation for differences in treatment efficacy.
- c. **TAK-733-resistant cells exhibited increased survival abilities compared with parental cell lines:** In addition, they established drug-resistant PNF cell lines from parental ipNF05.5 and ipNF9511.bc cells through chronic treatment with low-concentration TAK-733 to address the mechanism of drug resistance after MEKi monotherapy and to further evaluate the potential synergistic effects in reducing tumor growth. Drug resistance to TAK-733 was obtained, and ipNF05.5R and ipNF9511.bcR cells exhibited significantly higher viability than parental cells according to CCK-8 assay.
- d. **Dinaciclib was identified as a promising agent in combination with TAK-733:** TAK-733-resistant tumor cells had higher CDK1 expression than parental cells, demonstrated by western blot. The expression of survivin was also higher in these cells than in parental cells, suggesting that the resistant cells developed inhibited apoptosis after the induction of resistance. This result is consistent with their drug screening results and RNA sequencing analysis because CDK1 was one of the identified targets of dinaciclib. Dinaciclib may become a promising therapeutic agent for PNFs, especially when resistance occurs.
- e. **The dinaciclib in combination with TAK-733 demonstrated efficacy in treating patient-derived xenograft PNF mouse model:** Wang et al. (2021) also evaluated the in vivo efficacy of the combination treatment (CDK inhibitor [CDKi] dinaciclib with TAK-733) by generating a patient-derived xenograft model by grafting freshly extracted PNF tissue onto NSG mice. The mice were first given trametinib (1 mg/kg), TAK-733 (30 mg/kg), or control medium daily by gavage for 4 weeks. After administration, TAK-733 significantly reduced the tumor weight by 50–60% compared with the control treatment. Trametinib also showed a trend for decreasing tumor weight, although it was not statistically significant. They also evaluated the effectiveness of combination therapy with the CDKi dinaciclib (the combination group). After intraperitoneal injection of dinaciclib (20 mg/kg) three times a week over a 4-week treatment cycle, the tumors in the combination group were significantly reduced compared with those in the TAK-733 monotherapy group.

**ORCIDiDs**

Fabio Stefano Frech, <https://orcid.org/0000-0002-0689-6464>  
 Keyvan Nouri, <https://orcid.org/0000-0002-9950-8685>

## REFERENCES

- Aalborg J, Morelli JG, Mokrohisky ST, Asdigian NL, Byers TE, Dellavalle RP, et al. Tanning and increased nevus development in very-light-skinned children without red hair. *Arch Dermatol* 2009;145:989–96.
- Abramowicz A, Gos M. Neurofibromin in neurofibromatosis type 1 - mutations in NF1 gene as a cause of disease. *Dev Period Med* 2014;18:297–306.
- Ahsan S, Ge Y, Tainsky MA. Combinatorial therapeutic targeting of BMP2 and MEK-ERK pathways in NF1-associated malignant peripheral nerve sheath tumors. *Oncotarget* 2016;7:57171–85.
- Allaway RJ, Gosline SJ, La Rosa S, Knight P, Bakker A, Guinney J, et al. Cutaneous neurofibromas in the genomics era: current understanding and open questions. *Br J Cancer* 2018;118:1539–48.
- Allen B, Rader C, Babigian A. Giant lipomas of the upper extremity. *Can J Plast Surg* 2007;15:141–4.
- Aust MC, Spies M, Kall S, Jokuszies A, Gohritz A, Vogt P. Posttraumatic lipoma: fact or fiction? *Skinmed* 2007;6:266–70.
- Becker DW Jr. Use of the carbon dioxide laser in treating multiple cutaneous neurofibromas. *Ann Plast Surg* 1991;26:582–6.
- Belgam Syed SY, Lipoff JB, Chatterjee K. Acrochordon. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2021.
- Brenaut E, Nizery-Guermeur C, Audebert-Bellanger S, Ferkal S, Wolkenstein P, Misery L, et al. Clinical characteristics of pruritus in neurofibromatosis 1. *Acta Derm Venereol* 2016;96:398–9.
- Burt AM, Huang BK. Imaging review of lipomatous musculoskeletal lesions. *SICOT J* 2017;3:34.
- Canavese F, Krajchich JJ. Resection of plexiform neurofibromas in children with neurofibromatosis type 1. *J Pediatr Orthop* 2011;31:303–11.
- Chamseddin BH, Hernandez L, Solorzano D, Vega J, Le LQ. Robust surgical approach for cutaneous neurofibroma in neurofibromatosis type 1. *JCI Insight* 2019;5, e128881.
- Chamseddin BH, Le LQ. Management of cutaneous neurofibroma: current therapy and future directions. *Neurooncol Adv* 2019;2(Suppl. 1):i107–16.
- Charifa A, Azmat CE, Badri T. Lipoma pathology. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2021.
- Creytens D. A contemporary review of myxoid adipocytic tumors. *Semin Diagn Pathol* 2019;36:129–41.
- De Giorgi V, Gori A, Greco A, Savarese I, Alfaioli B, Grazzini M, et al. Sun-protection behavior, pubertal development and menarche: factors influencing the melanocytic nevi development—the results of an observational study of 1,512 children. *J Invest Dermatol* 2018;138:2144–51.
- Dombi E, Baldwin A, Marcus LJ, Fisher MJ, Weiss B, Kim A, et al. Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. *N Engl J Med* 2016;375:2550–60.
- Dulon M, Weichenthal M, Blettner M, Breitbart M, Hetzer M, Greinert R, et al. Sun exposure and number of nevi in 5- to 6-year-old European children. *J Clin Epidemiol* 2002;55:1075–81.
- El Safoury OS, Fawzy MM, Hay RM, Hassan AS, El Maadawi ZM, Rashed LA. The possible role of trauma in skin tags through the release of mast cell mediators. *Indian J Dermatol* 2011;56:641–6.
- FDA. KOSELUGO (selumetinib) capsules, for oral use Initial U.S. Approval: 2020. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/213756s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213756s000lbl.pdf); 2020 (accessed 24 September 2021).
- Ferner RE, O'Doherty MJ. Neurofibroma and schwannoma. *Curr Opin Neurol* 2002;15:679–84.
- Fiore M, MacNeill A, Gronchi A, Colombo C. Desmoid-type fibromatosis: evolving treatment standards. *Surg Oncol Clin N Am* 2016;25:803–26.
- Fiore M, Rimareix F, Mariani L, Domont J, Collini P, Le Péchoux C, et al. Desmoid-type fibromatosis: a front-line conservative approach to select patients for surgical treatment. *Ann Surg Oncol* 2009;16:2587–93.
- Fornage BD, Tassin GB. Sonographic appearances of superficial soft tissue lipomas. *J Clin Ultrasound* 1991;19:215–20.
- Friedrich RE, Schmelzle R, Hartmann M, Fünsterer C, Mautner VF. Resection of small plexiform neurofibromas in neurofibromatosis type 1 children. *World J Surg Oncol* 2005a;3:6.
- Friedrich RE, Schmelzle R, Hartmann M, Fünsterer C, Mautner V-F. Subtotal and total resection of superficial plexiform neurofibromas of face and neck: four case reports. *J Craniomaxillofac Surg* 2005b;3:55–60.
- Ganeshan D, Amini B, Nikolaidis P, Assing M, Vikram R. Current update on desmoid fibromatosis. *J Comput Assist Tomogr* 2019;43:29–38.
- Gross AM, Wolters PL, Dombi E, Baldwin A, Whitcomb P, Fisher MJ, et al. Selumetinib in children with inoperable plexiform neurofibromas [published correction appears in *N Engl J Med* 2020;383:1290]. *N Engl J Med* 2020;382:1430–42.
- Gutmann DH. Recent insights into neurofibromatosis type 1: clear genetic progress. *Arch Neurol* 1998;55:778–80.
- Harrison SL, MacLennan R, Buettner PG. Sun exposure and the incidence of melanocytic nevi in young Australian children. *Cancer Epidemiol Biomarkers Prev* 2008;17:2318–24.
- Jokinen CH, Argenyi ZB. Atypical neurofibroma of the skin and subcutaneous tissue: clinicopathologic analysis of 11 cases. *J Cutan Pathol* 2010;37:35–42.
- Jouhilahti EM, Peltonen S, Callens T, Jokinen E, Heape AM, Messiaen L, et al. The development of cutaneous neurofibromas. *Am J Pathol* 2011;178:500–5.
- Kasper B, Baumgarten C, Garcia J, Bonvalot S, Haas R, Haller F, et al. An update on the management of sporadic desmoid-type fibromatosis: a European Consensus Initiative between Sarcoma Patients EuroNet (SPAEN) and European Organization for Research and Treatment of Cancer (EORTC)/Soft Tissue and Bone Sarcoma Group (STBSG). *Ann Oncol* 2017;28:2399–408.
- Kim DH, Hyun DJ, Piquette R, Beaumont C, Germain L, Larouche D. 27.12 MHz radiofrequency ablation for benign cutaneous lesions. *BioMed Res Int* 2016;2016:6016943.
- Kincannon J, Boutzale C. The physiology of pigmented nevi. *Pediatrics* 1999;104:1042–5.
- Kolb L, Yarrarapu SNS, Ameer MA, Rosario-Collazo JA. Lipoma. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2021.
- Koskenvuo L, Ristimäki A, Lepistö A. Comparison of sporadic and FAP-associated desmoid-type fibromatoses. *J Surg Oncol* 2017;116:716–21.
- Kriechbaumer LK, Susani M, Kircher SG, Distelmaier K, Happak W. Comparative study of CO<sub>2</sub>- and Er:YAG laser ablation of multiple cutaneous neurofibromas in von Recklinghausen's disease. *Lasers Med Sci* 2014;29:1083–91.
- Lacka DE, Nasierowska-Guttmejer A. Fibromatosis - immunohistochemical evaluation, differential diagnosis from gastrointestinal tumors, and other mesenchymal tumours. *Prz Gastroenterol* 2019;14:79–85.
- Lassmann H, Jurecka W, Lassmann G, Gebhart W, Matras H, Watzek G. Different types of benign nerve sheath tumors. Light microscopy, electron microscopy and autoradiography. *Virchows Arch A Pathol Anat Histol* 1977;375:197–210.
- Lever WF, Schaumburg-Lever G. *Histopathology of the skin*. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 1990.
- Luther H, Altmeyer P, Garbe C, Ellwanger U, Jahn S, Hoffmann K, et al. Increase of melanocytic nevus counts in children during 5 years of follow-up and analysis of associated factors. *Arch Dermatol* 1996;132:1473–8.
- Lutterodt CG, Mohan A, Kirkpatrick N. The use of electrodesiccation in the treatment of cutaneous neurofibromatosis: a retrospective patient satisfaction outcome assessment. *J Plast Reconstr Aesthet Surg* 2016;69:765–9.
- Magro G, Amico P, Vecchio GM, Caltabiano R, Castaing M, Kacerovska D, et al. Multinucleated floret-like giant cells in sporadic and

- NF1-associated neurofibromas: a clinicopathologic study of 94 cases. *Virchows Arch* 2010;456:71–6.
- Markham A, Keam SJ. Selumetinib: first approval. *Drugs* 2020;80:931–7.
- Marks JG Jr, Miller JJ. Lookingbill and Marks' principles of dermatology. Amsterdam, The Netherlands: Elsevier; 2019.
- Massachusetts General Hospital. Ranibizumab for neurofibromas associated with neurofibromatosis type 1. <https://clinicaltrials.gov/ct2/show/NCT00657202>; 2008 (accessed 26 September 2021).
- Melosky B, Bradbury P, Tu D, Florescu M, Reiman A, Nicholas G, et al. Selumetinib in patients receiving standard pemetrexed and platinum-based chemotherapy for advanced or metastatic KRAS wildtype or unknown non-squamous non-small cell lung cancer: a randomized, multicenter, phase II study. Canadian Cancer Trials Group (CCTG) IND. 219. *Lung Cancer* 2019;1339:45–55.
- National Cancer Institute. Selumetinib in treating patients with neurofibromatosis type 1 and cutaneous neurofibroma. <https://ClinicalTrials.gov/ct2/show/NCT02839720>; 2016 (accessed 24 September 2021).
- Oliveria SA, Satagopan JM, Geller AC, Dusza SW, Weinstock MA, Berwick M, et al. Study of nevi in Children (SONIC): baseline findings and predictors of nevus count. *Am J Epidemiol* 2009;169:41–53.
- Orlow I, Satagopan JM, Berwick M, Enriquez HL, White KA, Cheung K, et al. Genetic factors associated with naevus count and dermoscopic patterns: preliminary results from the Study of Nevi in Children (SONIC). *Br J Dermatol* 2015;172:1081–9.
- Ortonne N, Wolkenstein P, Blakeley JO, Korf B, Plotkin SR, Riccardi VM, et al. Cutaneous neurofibromas: current clinical and pathologic issues. *Neurology* 2018;91(Suppl. 1):S5–13.
- Ostertag JU, Theunissen CC, Neumann HA. Hypertrophic scars after therapy with CO<sub>2</sub> laser for treatment of multiple cutaneous neurofibromas. *Dermatol Surg* 2002;28:296–8.
- Ragunatha S, Anitha B, Inamadar AC, Palit A, Devarmani SS. Cutaneous disorders in 500 diabetic patients attending diabetic clinic. *Indian J Dermatol* 2011;56:160–4.
- Riccardi VM. Mast-cell stabilization to decrease neurofibroma growth. Preliminary experience with ketotifen. *Arch Dermatol* 1987;123:1011–6.
- Riccardi VM. An overview of NF-1: dysplasia and neoplasia. In: Riccardi VM, editor. *Neurofibromatosis: phenotype, natural history, and Pathogeneis*. Baltimore, MD: The John Hopkins University Press; 1992. p. 28–33.
- Riccardi VM. A controlled multiphase trial of ketotifen to minimize neurofibroma-associated pain and itching. *Arch Dermatol* 1993;129:577–81.
- Robertson KA, Nalepa G, Yang FC, Bowers DC, Ho CY, Hutchins GD, et al. Imatinib mesylate for plexiform neurofibromas in patients with neurofibromatosis type 1: a phase 2 trial. *Lancet Oncol* 2012;13:1218–24.
- Rogers T, Marino ML, Raciti P, Jain M, Busam KJ, Marchetti MA, et al. Biologically distinct subsets of nevi. *G Ital Dermatol Venereol* 2016;151:365–84.
- Salam GA. Lipoma excision. *Am Fam Physician* 2002;65:901–4.
- Schaffer JV. Update on melanocytic nevi in children. *Clin Dermatol* 2015;33:368–86.
- Shiurba RA, Eng LF, Urich H. The structure of pseudomeissnerian corpuscles. An immunohistochemical study. *Acta Neuropathol* 1984;63:174–6.
- Tong KN, Seltzer S, Castle JT. Lipoma of the parotid gland. *Head Neck Pathol* 2020;14:220–3.
- Vetrano IG, Saletti V, Nazzi V. Fluorescein-guided resection of plexiform neurofibromas: how I do it. *Acta Neurochir (Wien)* 2019;161:2141–5.
- Vranceanu AM, Merker VL, Park E, Plotkin SR. Quality of life among adult patients with neurofibromatosis 1, neurofibromatosis 2 and schwannomatosis: a systematic review of the literature. *J Neurooncol* 2013;114:257–62.
- Walker EA, Petscavage JM, Brian PL, Logie CJ, Montini KM, Murphey MD. Imaging features of superficial and deep fibromatoses in the adult population. *Sarcoma* 2012;2012:215810.
- Wang W, Cui X-W, Gu Y-H, Wei C-J, Li Y-H, Ren J-Y, et al. Combined cyclin-dependent kinase inhibition overcomes MAPK/extracellular signal-regulated kinase kinase inhibitor resistance in plexiform neurofibroma of neurofibromatosis type I. *J Invest Dermatol* 2021. <https://doi.org/10.1016/j.jid.2021.07.164> (accessed 24 September 2021).
- Weiss LM. Chapter 46: Soft tissues. In: Weidner N, Cote R, Suster S, Weiss L, editors. *Modern surgical pathology*. 2nd ed. Philadelphia, PA: Saunders; 2009. p. 1717–83.
- Wiecker TS, Luther H, Buettner P, Bauer J, Garbe C. Moderate sun exposure and nevus counts in parents are associated with development of melanocytic nevi in childhood: a risk factor study in 1,812 kindergarten children. *Cancer* 2003;97:628–38.
- Woodruff JM. Pathology of tumors of the peripheral nerve sheath in type 1 neurofibromatosis. *Am J Med Genet* 1999;89:23–30.
- Yeh I, McCalmont TH. Distinguishing neurofibroma from desmoplastic melanoma: the value of the CD34 fingerprint. *J Cutan Pathol* 2011;38:625–30.